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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/300,425	04/28/99	NERI	D 113000.301

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EXAMINER	
PORTNER,V	
ART UNIT	**PAPER NUMBER**
1645	15

DATE MAILED: 09/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/300,425	Neri et al
Examiner	**Group Art Unit**
Portner	1645

☒ Responsive to communication(s) filed on *Sep 1, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *14-17 and 19-27* is/are pending in the application.

Of the above, claim(s) *14-17, 19, and 25-27* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *14-17 and 19-27* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7,10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-13 and 18 have been canceled.

Claims 14-17, 19-27 are pending.

Claims 20-24 are under consideration.

Claims 14-17, 19 and 25-27 are withdrawn from consideration.

Election/Restriction

1. Claims 14-17 and 19, 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II and III, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper Number 13, Dated September 1, 2000.

2. Applicant's election with traverse of Group I, claims 1-13 and 18, 20-24, classified in class 530, subclass 387.1 in Paper No. 13, Dated September 1, 2000 is acknowledged. The traversal is on the ground(s) that "The Examiner has not provided sufficient basis to substantiate this restriction". This is not found persuasive for the reasons below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1)independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the inventions of Groups I-III are drawn to distinct inventions which are related as separate products, and methods capable of separate functions. Restrictions between the inventions is deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. In the instant case a burden has been established in showing that the inventions of Groups I-III are classified separately necessitating different searches of issued US Patents. However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example many types of methods of using antibodies are individually patentable. Additionally, it is submitted that the inventions of Groups I-III have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made Final.

Information Disclosure Statement

3. The information disclosure statements filed September 28, 1999 and April 13, 2000 have been considered as to the merits prior to first action.

Specification

4. The Amendment submitted September 1, 2000 has been entered in part. The portions of the Amendment not entered were those directed to page 27. Submission of a new table with the appropriate changes, insertion of SEQ ID Nos, is requested.

5. The Amendment of claim 10, at lines 2, 7 and 9 was not entered because the claim has been canceled by Applicant in the response to Restriction requirement submitted on September 1, 2000.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

7. The Brief Description of the Drawings section has been amended to recite SEQ ID No, but how these numbers

correspond to each sequence designated --a through h-- is not clear from the amendment provided. Clarification of the amendment to refer to each sequence by the designations given could provide for one to one correspondence. For example: Figure 1, --sequences a through h,-- "SEQ ID NO 11-18, respectively".

Claim Rejections - 35 U.S.C. § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 20 depends from canceled claim 1, if claim 20 were amended to recite the claim limitations of claim 1, would contain the phrase "improved affinity to said ED-B epitope". A point of reference for antibody binding has not been defined in the claims. Therefore, how the affinity is improved is not distinctly claimed. The term " improved" in claim 1 is a relative term which renders the claim indefinite. The term "improved" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

b. The phrase "said ED-B epitope" recited on line 2 of claim 1 lacks antecedent basis in claim 1, line 1. No specific epitope is defined, any epitope that is characteristic of the ED-B is recited in line one of the claim. What defines a characteristic epitope is not distinctly claimed.

c. Claim 20, if amended to recite the claim limitations of claim 1, from which it now depends, would recite an abbreviation "ED-B". Abbreviations must be defined at their first appearance ~~appearing~~ in the claims in order for the claimed invention to be clear. Clarification of each abbreviation recited is requested.

d. Claims 20-24 all recite the phrase "capable of". This does not distinctly claim applicant's invention. Amendment of the claim to recite positive claim limitations could obviate this rejection.

Claim Rejections - 35 U.S.C. § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

11. Claims 20-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Mariani et al (December 15, 1997).

The reference discloses a monoclonal antibody that specifically binds to the human isoform of Fibronection extra domain B+ present in the oncofetal domain. The antibody was radiolabeled and used in vivo to visualize malignant brain tumor tissue growth. The radiolabeled antibody was indicated as useful in diagnosis, specifically for immunoscintigraphy in cancer patients. Inherently the disclosed antibody- radiolabel conjugate anticipates the now claimed invention.

12. Claims 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al (WO97/45544, reference provided in Applicant's 1449).

Neri et al disclose antibody conjugates as diagnostic agents, to deliver cytotoxic agents in vivo and to trigger coagulation within new blood vessels resulting in tumor cell starvation. (see page 16, lines 13-18).

Recombinant polypeptide antibodies, specifically scFv antibodies, that specifically bind to Fibronection ED-B domain with high affinity (see claim 14) conjugated to a photosensitive agent, Cy7 (see page 36, line 23), as well as conjugates of an antibody to radiolabels (radioactive iodine, Tc^{99}, In^{111} ,see pages 15-16, especially page 16, line 16), fluorochrome, phosphor, laser dye, fluorescein, rhodamine, phycoerythrin, Texas Red or diaminobenzidine, colored, magnetic, paramagnetic, and biologically or chemically active agents (see page 15, lines 8-11, lines 15-17, lines 18-21) are disclosed.

Conjugates, of photosensitizer Cy7 to a scFv antigen binding reagent specific to fibronection ED-B domain, were produced (see page 38, lines 28-31). Cy7 produces fluorescence at greater than 760 nm and is read by a computer controlled CCD-camera (See page 36, lines 18-29). Covalent linkages join antibodies to the second molecule in the conjugates disclosed. The reference inherently anticipates the now claimed invention.

13. Claim 20 is rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 6,093,399; filing date June 7, 1995).

Thorpe et al claims a conjugate that comprises an antibody and a molecule capable of inducing blood coagulation and blood vessel occlusion, wherein the antibody (first binding region to be an antigen binding region of an antibody) is specific for a tumor associated fibronectin isoform and the coagulation factor is either Vitamin K-dependent coagulation factor that lacks the Gla modification or Tissue factor (TF).

The tumor associated fibronectin isoform is taught to comprise the ED-B Oncofetal Domain (see page 5, col. 2, Castellani et al reference, 1994).

Inherently the reference anticipates the now claimed conjugates.

14. Claim 20 is rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 5,877,289; filing date June 7, 1995).

Thorpe et al claim conjugate (binding ligand) that comprises an antibody (binding region) and a coagulation factor. Thorpe (claims 48 and 60) define the antibody (first binding region to be an antigen binding region of an antibody) as specific for a tumor associated fibronectin isoform. The tumor associated fibronectin isoform is taught to comprise the ED-B Oncofetal Domain (see page 3, col. 1, near bottom, Carnemolla et al, 1989 and 1992 references). Therefore, the claimed conjugate comprises an antigen binding region of an antibody that specifically binds to fibronection ED-B oncofetal domain.

The claimed conjugate comprises an antigen binding region of an antibody specific for ED-B and a Tissue factor (TF) molecule, a molecule disclosed that is capable of inducing blood coagulation and blood vessel occlusion.

Inherently the reference anticipates the now claimed conjugates.

Claim Rejections - 35 U.S.C. § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claim 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544, reference provided in Applicant's 1449) in view of Theodore et al (US Pat. 6,015,897).

See discussion of Neri et al above. Neri et al suggest and teach the formulation of conjugates for delivery of cytotoxic agents, and for the delivery of conjugates to trigger coagulation within new blood vessels resulting in indirect tumor therapy (see page 16, lines 13-26), as well as show the use of photosensitive fluorescent labels that absorb at a wavelength above 600 nm but differs from the instantly claimed invention by failing to show the formulation of a conjugate that comprises photosentizing agent tin (IV)chlorine e6.

Theodore et al teach the use of tin chlorin e6, an exemplary chlorin photosensitizing agent, in the production conjugates (col. 50, line 14 and lines 26-35) in an analogous art for the purpose producing effective tumor targeted photodynamic therapy reagents (see col. 49, lines 13-35, especially line 24). Conjugates that comprise this type of photosensitizing agent evidence a strong absorption between 600 and 700 nm (see col. 49, lines 13-14). Tin chlorin e6 is a porphyrin compound that effectively destroys target cells (see col. 49, lines 13-35) when formulated into a photosensitizing photodynamic conjugate reagent.

In view of the teachings of Theodore et al that tin chlorin e6 is an effective photodynamic, photosensitizing reagent for killing cells when conjugated to an antibody (anti-ligand, col. 48, lines 38-46), the person of ordinary skill in the art at the time the invention was made would have been motivated to modify the conjugates of Neri to include the tin-chlorin e6 photosensitizing agent of Theodore because Neri teaches ED-B oncofetal domain specific antibodies for the targeting, killing

or starving of tumor cells (starvation is triggered through coagulation within new blood vessels resulting in indirect tumor therapy) when conjugated to a photosensitizing molecule. Theodore discloses effective photosensitizing reagents that work to selectively kill tumor cells resulting in an improved targeting ratio or increased absolute dose to the target cell sites in comparison to conventional cancer therapy (col. 1, lines 42-47), as well as provides non-target tissue with reduced exposure to the photosensitizing agent (see col. 1, lines 48-65).

In the absence of a showing of unexpected results, the teaching of the prior art obviate the now claimed invention.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

18. **Koukoulis et al** (Feb 1995, abstract) is cited to show monoclonal antibodies that specifically binds to Fibronection extra domain B+ and the oncofetal isoforms of cellular fibronectin.

19. **JP-4169195** is cited to show an radioimmunoassay for Fibronectin ED-B domain.

20. **Trauner et al** (US Pat. 5,942,534, US Pat. 5,913,884); **Dolphin et al** (US Pat. 5,831,088, US Pat. 5,648,485) are cited to show chlorins as photosensitizing agents.

21. Thorpe et al (US Pat. 6,004,555) is cited to show methods specific for coagulation of vasculature.

This is a non-final action.

No claims are allowed.

22.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

L. F. Smith

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August 18, 2000